DETAILED ACTION

1. Applicants' arguments, filed October 11, 2011, have been fully considered but they are not deemed to be fully persuasive. The following rejections and/or objections constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 - 2nd Paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 6 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 6 and 23 recite the limitation "said aroma substance" in line 2. There is insufficient antecedent basis for this limitation in the claim.

4. Claim 34 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 34 depends from claim 33, which was cancelled in the most recent set of claim amendments. Therefore, the metes and bounds of this claim cannot be determined, rendering this claim indefinite.

As the limitation from claim 33 has been incorporated into claim 1, for the purposes of applying art below, claim 34 is being interpreted as depending from claim 1.

5. Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 35 recites the limitation "said at least one active substance" in lines 1 - 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112 - 4th Paragraph

6. The following is a quotation of the fourth paragraph of 35 U.S.C. 112:

> Subject to the [fifth paragraph of 35 U.S.C. 112], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

7. Claim 35 is rejected under 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. Claim 35 specifically excludes a pharmaceutical active substance from being present in the administration form. Amended claim 1, from which claim 35 depends, requires the presence of at least one pharmaceutical active substance in a salt form. Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form,

rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kigasawa et al. (US 4,572,832) in view of Lydzinski et al. (US 2003/0099691).

Kigasawa et al. discloses soft buccal compositions which comprise a medicament to be absorbed through the oral cavity, a water-soluble protein, a polyhydric alcohol and a fatty acid ester and/or a carboxyvinyl polymer (col 1, ln 36 – 49). Forms include sheets, bands and disks (col 6, ln 21 – 26). A variety of active agents including some that are salts, such as triperizone hydrochloride, dantrolene sodium and ipratropium bromide, can be included in the buccal dosage forms (col 1, ln 57 - col 2, ln 64). In example 8 (col 12, ln 43 – 60), a soft buccal comprising the active ingredient pindolol is prepared using the film forming polymer gelatin (gelatine), pH 6.5 phosphate buffer and the excipients propylene glycol, medium-chain fatty acid triglycerides, sucrose fatty acid ester glycerin, mannitol and corn starch. The total weight of the excipients is about 70% of the total weight. After sonication to create a dispersion, the gelatin was added and the resulting mixture kneaded and cut into plate-shaped (a film-shaped) dosage form. This dosage form took between 16 minutes and 17 minutes, 15 seconds to disintegrate. In example 8(a) (col 12, ln 24 – 42), gelatin was dissolved in water to which a pindolol dispersion was added, which was cut into pieces and dried to a plate like shape which was 17 mm long, 9 mm wide and 2 mm thick. This plate-shaped form took between 10 minutes, 30 seconds and 12 minutes, 40 seconds

to disintegrate. Additives can be added in addition to the required ingredients, including flavorings (aroma substances) such as menthol, lemon oil and citrus flavor as well as other excipients, disintegrating adjusting agents, emulsifiers, dispersants, binders and thickeners (col 5, ln 56 – col 6, ln 6). The required polyhydric alcohol component can be ingredients such as ethylene glycol, propylene glycol, polyethylene glycol (col 4, ln 9 – 10). Also included in the category of polyhydric alcohols are cellulose and cellulose derivatives such as methyl cellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxyethylcellulose and carboxymethyl cellulose, and polysaccharides such as alginic acid (col 4, ln 18 – 49).

Kigasawa et al. does not disclose one of the listed matrix forming polymers.

Lydzinski et al. discloses an oral film that useful for delivering an agent to an animal or human to produce either a therapeutic or cosmetic effect, such as breath fresheners or fragrances (¶ [0006]), both of which read on the aroma substance of the instant claims. The active agent can be used in any amount desired, the only limitation being the potential load of the film, but generally, the amounts used will range from about 0.5% to about 15%, with substantially higher amounts for breath fresheners than for pharmaceutical agents (¶ [0024]). The oral film can be comprised of starch, but the starch component can also comprise cellulosic material or gums such as alginate, pullulan, carboxymethyl cellulose or carrageenan that is generally present in amount of from about 50 % to 100% exclusive of the active agent (¶ [0022]). The use of carrageenan will produce a mucoadhesive administration form.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate an aroma substance in place of the pharmaceutically active ingredient in the compositions of Kigasawa et al. and to use substances such as pullulan or carrageenan as the base mass material to produce a disintegrating oral film. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because the inclusion of an aroma substance (breath freshener or fragrance) results in an oral film that quickly disintegrates in the mouth, leaving the user with fresh or scented breath. Carrageenan and pullulan are taught as functionally equivalent to the cellulose and alginic acid materials of Kigasawa et al. and can also be used in oral film masses.

The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. As Lydzinski et al. teaches, almost any amount of active substance can be present in the film and the type of active ingredient will determine how much is added, with pharmaceutically active substances generally being present in lower amounts than breath freshener ingredients, so one would determine the optimal amount to add based on the particular active ingredient that is used and desired effect. The amount of matrix-forming polymer will in part determine the properties of the film, such as how it takes to dissolve. A faster

dissolving film will release the active/aroma substances quickly and allow the user to eat or drink soon after taking the film without having to wait for prolonged periods of time. A shorter the disintegration time in the mouth would make it less likely that the remaining portion of the administration form would be swallowed.

In regards to the claim limitation of "in a manner avoiding mucosal irritation", a review of the instant application revealed no features of the dosage form beyond the pH that reduces mucosal irritation and thus the person having ordinary skill in the art would necessarily prepare such a form when they prepare a dosage form whose pH is approximated or adapted to the physiological pH value of the mucosa to which the film will be applied.

12. Claims 1, 4 - 6, 8 - 11, 13, 14, 21 - 29, 34, 35 and 37 - 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kigasawa et al. (US 4,572,832) in view of Lydzinski et al. (US 2003/0099691) and Rault et al. (US 5,900,247). This rejection is MAINTAINED for the reasons of record set forth in the Office Action mailed July 19, 2011 and those set forth below.

In regards to the new claim limitation of "in a manner avoiding mucosal irritation", a review of the instant application revealed no features of the dosage form beyond the pH that reduces mucosal irritation and thus the person having ordinary skill in the art would necessarily prepare such a form when they prepare a dosage form whose pH is approximated or adapted to the physiological pH value of the mucosa to which the film will be applied.

Amended claims 6 and 23 are being interpreted as requiring the presence of both a pharmaceutical active substance in the salt form and an aroma substance. Kigasawa teaches that additives such as the flavorings menthol or lemon oil, which read on aroma substances, are possible additives (col 5, ln 56 - col 6, ln 6). Lydzinski et al. teaches that active agents including breath fresheners, aromatizing agents, flavors or fragrances can be delivered (¶ [0024]), which reads on aroma substances. By combining a salt form active agent and an aroma substance, a form that provides both freshening and a therapeutic effect will be prepared.

In regards to claim 39, the peelable protective film of Rault is different in active substance concentration as the administration layer contains active ingredient while the protective layer contains none.

Applicant traverses this rejection on the grounds that example 8(b) of Kigasawa et al. uses an active ingredient that is not present in a salt form and so fails to teach pH adjustment in the case where the pharmaceutical active substance is present in salt form. One skilled in the art would clearly understand that the use of phosphate buffer 6.5 is necessitated by the special mixture of ingredients in this example.

These arguments are unpersuasive. Kigasawa et al. teaches that a variety of active agents including some that are salts, such as triperizone hydrochloride, dantrolene sodium and ipratropium bromide, can be included in the buccal dosage forms (col 1, ln 57 - col 2, ln 64). Merely because the example that uses phosphate buffer has a drug that is not in the salt form does not mean that phosphate buffer can only be used in the specific combination set forth in the example. No differentiation in

the formulations for the non-salt forms and salt forms is taught by the art. The knowledge of the person of ordinary skill would indicate that the pH of the base should be approximated or adapted to the intended use location, and the particular active substance and the form of the active substance can alter the pH of the base mass. If the particular drug, in the free form or as a salt, and matrix materials selected for the dosage form results in a base mass having a pH adapted or approximated to the intended use location, it is not necessary to include a buffer and/or pH adjusters in the formulation. If the combination of drug and matrix materials do not result results in a base mass having a pH adapted or approximated to the intended use location, the person of ordinary skill in the art would adjust the pH of the base mass using a material such as the phosphate buffer used in example 8(b).

Applicant also argues that new claim 37 further limits the pH to 8 to 9 and about 4, further differentiating the claims from the cited prior art.

These arguments are unpersuasive. It is noted that the only numerical pH values recited in claim 37 is about 4 but claim 38 contains the same list of pH values as in claim 1. With the exception of claims 24 and 25, the pH values recited in the claims are not the pH value that is required for the base mass. Rather, these claims require that the pH value of the base mass be “approximated or adapted to the physiological pH value of the mucosa to which the administration form is to be applied” and the pH values given specify the physiological pH range of various mucosa, not the actual pH of the base mass of the material. The applied art teaches buccal dosage forms and the person of ordinary skill in the art would realize that an administration form having a pH

incompatible with the intended administration location would lead to irritation, e.g. prolonged contact with an acidic dosage form in the mouth would cause irritation but not in the stomach, that has a more acidic physiological pH, and thus approximate or adapt the pH of the base mass of the dosage form for the intended use location of the dosage form.

Applicant argues that Lydzinski teaches films containing starch as the main component and only in such compositions are carrageenan, pullulan, cellulosic materials and alginate taught as functionally equivalent. Those ingredients are optional and added in minor amounts and the reference also indicates that these substances have properties which are different from starch and thus these substances are not equivalent to starch either.

These arguments are unpersuasive. Lydzinski et al. discloses that for these polymers, not more than 15 percent by weight of the starch component is included (¶ [0022]), amounts which are not necessarily “minor amounts”. The instant claims do not exclude the presence of starch from the base mass, and only claims 4 and 21 require specific amounts of the polymers recited in claim 1 to be present in the final dosage form. The art teaches that the various polymers are materials, either alone or in combination, that can be used to form that carrier/matrix for dried films, particularly those for oral or buccal use, and thus are functionally equivalent, even if the various polymers do not share all the exact features.

Applicant also argues that the teachings of the present application exclude the peelable protective film from being an additional layer in the multilayer administration

form. The specification indicates that the polymeric matrix can consist of multiple layers (e.g., ¶¶ [00024] and [00050]). The peelable protective film does not meet the criteria in claim 39 since it contains neither active substances nor additives.

These arguments are unpersuasive. The cited portions of the specification do not provide a limiting definition of peelable film and the cited sections indicates that at least one layer of the multilayer form contains an active substance, a limitation meet by the film administration form taught by Kigasawa with the backing layer of Rault. The peelable protective film of Rault is clearly different in active substance concentration as the administration form contains active ingredient while the protective layer contains none.

13. Claims 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keith et al. (US 4,764,378) in view of Lydzinski et al. (US 2003/0099691).

Keith et al. discloses buccal dosage forms for transmucosal administration of drugs (abstract) and thus the pH of the base mass of these dosage forms is approximated or adapted to the physiological values of the mucosa to which the administration form is to be applied. The matrix comprises about 20% to about 75% of a low molecular PEG (col 3, ln 16 – 24), about 2% to about 60% of a medium to high molecular weight PEG (col 3, ln 42 – 46), about 1% to about 40% of a high molecular PEG (col 3, ln 61 – 68), about 25% to about 40% of an auxiliary polymeric ingredient such as polyvinylpyrrolidone (col 4, ln 13 – 16), minor amounts of additional ingredients such as up to about 5% of plasticizer (col 4, ln 28 – 33) and between about 0.01% and

about 10% of active ingredient (col 5, ln 40 – 42). The base mass comprises PEG (polyethylene oxide) of varying molecular weights (100, 1450, 3350 and 8000); propylene glycol, a plasticizer (col 4, ln 31 - 33); and polyvinylpyrrolidone that when cut in a film, dissolves in less than 60 seconds when placed in the buccal pouch or sublingually (Example 1, col 6, ln 15 – 43). Alternatively, the high molecular weight ingredient can be sodium alginate or carboxymethyl cellulose (col 3, ln 66 - col 4, ln 12). In example 2, the base mass contains 5% of the plasticizer propylene glycol (col 6, ln 46 – 57). A variety of pharmaceutical active ingredients can be incorporated in the base material, including 5% verapamil hydrochloride (column 7, ln 1 – 6), a hydrochloride salt form of the active ingredient, resulting in a final formulation in which the polymer portion would be less than 95% (5% active ingredient, 3% propylene glycol). One formulation contained 10% by weight of the active ingredient verapamil free base (col 7, ln 38 – 42).

Keith et al. does not disclose one of the listed matrix forming polymers.

Lydzinski et al. discloses an oral film that useful for delivering an agent to an animal or human to produce either a therapeutic or cosmetic effect, such as breath fresheners or fragrances (¶ [0006]), both of which read on the aroma substance of the instant claims. The active agent can be used in any amount desired, the only limitation being the potential load of the film, but generally, the amounts used will range from about 0.5% to about 15%, with substantially higher amounts for breath fresheners than for pharmaceutical agents (¶ [0024]). The oral film can be comprised of starch, but the starch component can also comprise cellulosic material or gums such as alginate, pullulan, carboxymethyl cellulose or carrageenan that is generally present in amount of

from about 50 % to 100% exclusive of the active agent (¶ [0022]). The use of carrageenan will produce a mucoadhesive administration form.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate an aroma substance in place of the pharmaceutically active ingredient in the compositions of Keith et al. and to use substances such as pullulan or carrageenan in the base mass to produce a disintegrating oral film. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because the inclusion of an aroma substance (breath freshener or fragrance) results in an oral film that quickly disintegrates in the mouth, leaving the user with fresh or scented breath. Carrageenan and pullulan are taught as functionally equivalent to the cellulose and alginate materials of Keith et al. and can also be used in oral film masses.

The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. As Lydzinski et al. teaches, almost any amount of active substance can be present in the film and the type of active ingredient will determine how much is added, with pharmaceutically active substances generally being present in lower amounts than breath freshener ingredients, so one would determine the optimal amount to add based on the particular active

ingredient that is used and desired effect. The amount of matrix-forming polymer will in part determine the properties of the film, such as how it takes to dissolve. A faster dissolving film will release the active/aroma substances quickly and allow the user to eat or drink soon after taking the film without having to wait for prolonged periods of time. A shorter the disintegration time in the mouth would make it less likely that the remaining portion of the administration form would be swallowed.

In regards to the claim limitation of “in a manner avoiding mucosal irritation”, a review of the instant application revealed no features of the dosage form beyond the pH that reduces mucosal irritation and thus the person having ordinary skill in the art would necessarily prepare such a form when they prepare a dosage form whose pH is approximated or adapted to the physiological pH value of the mucosa to which the film will be applied.

14. Claims 1, 4 - 6, 9 - 11, 13, 14, 21 - 25, 27 - 29, 34, 35 and 37 - 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keith et al. (US 4,764,378) in view of Lydzinski et al. (US 2003/0099691) and Rault et al. (US 5,900,247). This rejection is MAINTAINED for the reasons of record set forth in the Office Action mailed July 19, 200 and those set forth herein.

In regards to the new claim limitation of “in a manner avoiding mucosal irritation”, a review of the instant application revealed no features of the dosage form beyond the pH that reduces mucosal irritation and thus the person having ordinary skill in the art would necessarily prepare such a form when they prepare a dosage form whose pH is

approximated or adapted to the physiological pH value of the mucosa to which the film will be applied.

Amended claims 6 and 23 are being interpreted as requiring the presence of both a pharmaceutical active substance in the salt form and an aroma substance. Lydzinski et al. teaches that active gents including breath fresheners, aromatizing agents, flavors or fragrances can be delivered (¶ [0024]), which reads on aroma substances. By combining a salt form active agent and an aroma substance, a form that provides both freshening and a therapeutic effect will be prepared.

In regards to claim 39, the peelable protective film of Rault is different in active substance concentration as the administration layer contains active ingredient while the protective layer contains none.

Applicant traverse this rejection on the grounds that Keith fails to teach pH measurement or adjustment and does not support the indirect conclusion that the pH of the base mass of these dosage forms must have been approximated or adjusted to the physiological values of the mucosa. Keith also fails to teach or disclose any measures or efforts to avoid irritation of the mucosa.

These arguments are unpersuasive. As discussed above in the rejection based on Kigasawa, the majority of the claims do not require any specific pH value for the base mass. The teachings of the reference must also be taken in light of the person having ordinary skill in the art that would approximate or adapt the matching of the pH of the administration form to the intended administration site. A review of the instant application revealed no features of the dosage form beyond the pH that reduces

mucosal irritation and thus the person having ordinary skill in the art would necessarily prepare such a form when they prepare a dosage form whose pH is approximated or adapted to the physiological pH value of the mucosa to which the film will be applied.

15. Claim 8 was rejected under 35 U.S.C. 103(a) as being unpatentable over Keith et al. in view of Lydzinski et al. and Rault et al. further in view of Bergeron et al. (WO 99/53897) and Gibson et al. (EP 0386960). This rejection is MAINTAINED for the reasons of record set forth in the Office action mailed July 19, 2011 and those set forth herein.

Applicant has not specifically addressed this rejection other than referring to the rejection of claim 8, so the rejection is maintained for the reasons set forth above with regard to Keith et al. in view of Lydzinski et al. and Rault et al.

16. Claim 26 was rejected under 35 U.S.C. 103(a) as being unpatentable over Keith et al. in view of Lydzinski et al. and Rault et al. further in view of Bergeron et al. and Gibson et al. further in view of Kigasawa et al. (US 4,572,832).

Applicant has not specifically addressed this rejection other than referring to the rejection of claim 26, so the rejection is maintained for the reasons set forth above with regard to Keith et al. in view of Lydzinski et al. and Rault et al. further in view of Bergeron et al. and Gibson et al.

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NISSA WESTERBERG whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nissa M Westerberg/
Primary Examiner, Art Unit 1618